Combined treatment with pegylated interferon-alpha-2a and dacarbazine in patients with advanced metastatic melanoma: a phase 2 study

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Abstract: BACKGROUND: Dacarbazine (DTIC) and pegylated interferon (IFN)-alpha-2a have both demonstrated some efficacy as single agents in metastatic melanoma. To the authors' knowledge, the current study is the first to test a combination of these 2 agents in a phase 2 trial. METHODS: Twenty-eight patients with stage IV melanoma without brain metastases were treated with DTIC (at a dose of 850 mg/m(2) every 3 weeks) combined with weekly pegylated IFN-alpha-2a at a dose of 180 microg. The study was initiated to evaluate the efficacy and tolerability of the combination. The primary study endpoint was objective response. RESULTS: Twenty-five patients were evaluable for response. Two patients (8.0%) achieved a complete response that continued for >480 days and 746 days, respectively. Four patients (16.0%) demonstrated a partial response, and another patient experienced stable disease. Six of 7 nonprogressive patients had either not received treatment or had not developed disease progression during adjuvant IFN treatment for stage II/III disease. The median duration of response was 236 days, the median progression-free survival was 56 days, and the overall survival time was 403 days. Few grade 3 toxicities and only 1 grade 4 toxicity were observed (according to National Cancer Institute Common Toxicity Criteria). CONCLUSIONS: The combination of DTIC and pegylated IFN-alpha-2a was found to be well tolerated in patients with metastatic melanoma. The response rate of 24%, including 2 long-lasting complete responses, is encouraging, but must be confirmed in larger trials.

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Combined treatment with pegylated Interferon α-2a and Dacarbazine in advanced metastatic melanoma: a phase II study

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Short title: Pegylated interferon α-2a and DTIC in melanoma

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Condensed abstract

This is the first report on a combined treatment with pegylated interferon α-2a and dacarbazine in metastatic melanoma. The regimen was well tolerated with an encouraging remission rate of 24%.

Abstract

Background: Dacarbazine (DTIC) and pegylated Interferon α-2a have both demonstrated some efficacy as single agents in metastatic melanoma. This study is the first to test a combination in a phase II trial.

Patients and methods: 28 stage IV melanoma patients without brain metastases were treated with DTIC (850mg/m^2 3-weekly) combined with weekly 180µg pegylated Interferon α-2a (Pegasys®). The study was initiated to evaluate the efficacy and tolerability of the combination. Primary study endpoint was objective response.

Results: 25 patients were evaluable for response. Two patients (8.0%) achieved a complete response ongoing for more than 480 and 746 days, respectively. Four patients (16.0%) demonstrated a partial response, another patient a disease stabilization. 6/7 non-progressive patients had either not received or not progressed during adjuvant interferon treatment for stage II/III. Median duration of response was 236 days, progression-free survival 56 days, and overall survival time was 403 days. Few grade 3 and only one grade 4 toxicity were observed.

Conclusions: The combination of DTIC and pegylated interferon α-2a was well tolerated in metastatic melanoma patients. The response rate of 24% including two long-lasting complete remissions is encouraging, but has to be confirmed in larger trials.

Key words: Dacarbazine, pegylated Interferon α-2a, metastatic melanoma

Introduction

Despite significant improvement in the early detection and treatment of malignant melanoma in recent years, there has been little progress in an enhancement of response rates and survival times in patients with advanced metastatic melanoma (AJCC classification, stage IV) [1]. The median survival time remains still in a range of 6 to 12 months [2]. Complete responses are limited to a small subset of patients which cannot be exactly characterized and predicted by now. After three decades of clinical trials Dacarbazine (DTIC) is still considered as a reference drug. Prospectively-randomized trials on DTIC as a single agent have demonstrated response rates in a range of 6 to 12% in the recent years without a clear impact on overall survival [3, 4]. Therefore, surgical resection of metastases and multidisciplinary approaches including radiotherapy for palliative care are still treatment options of first choice. Immunotherapeutic approaches using recombinant cytokines like interferons or interleukin-2 have not demonstrated a clear benefit to Dacarbazine alone. A biochemotherapy regimen containing Interferon α, Interleukin-2 and three different cytotoxic drugs (CVD scheme) has also failed to increase survival rates [overview in 2]. Therefore it is widely accepted that the therapy of choice in patients with advanced metastatic melanoma is a treatment within a clinical trial, in order to gain knowledge on new therapeutic options with more efficacy in this disease.

Recombinant interferons have been proven to demonstrate limited anti-tumor activity in patients with metastatic melanoma as single agents. Furthermore, they are widely used for the adjuvant treatment of malignant melanoma with benefits in relapse-free survival and small impact on overall survival [5-7].

The combination of Dacarbazine (DTIC) and recombinant Interferon α has been studied intensively during the last 15 years. Despite numerous clinical trials and a meta-analysis on this combination regimen, it appears that this combination is only affecting the response rate but not the overall survival time [8]. Therefore, there is a clear medical need for more effective drug

combinations. One potential disadvantage of recombinant interferons are the post-injectional peaks in the serum concentration which are associated with flu-like symptoms some hours after drug exposure. The relatively short half-life of recombinant interferon α required a new drug formulation which would be more acceptable for a long-term treatment and constant drug levels [9].

Recombinant human PegInterferon α-2a (PEG-IFNα-2a; Pegasys; Hoffmann-La Roche Inc., Nutley, ND, USA) is a form of Interferon α-2a modified by the covalent attachment of a branched 40-KD metoxipolyethyleneglucolmoiety. Already licensed for use in chronic hepatitis C, studies in this population found that PEG-IFNα-2a has superior efficacy compared to non-pegylated Interferon α. The long half-life of PEG-IFNα-2a allows a more convenient once-weekly dosing regimen with improved tolerability. Formation of binding or neutralizing antibodies against PEG-IFNα-2a is rare and occurs only in 2-6% of patients [10, 11]. Apart from phase I/II clinical trials conducted in renal cell cancer and hematologic malignancies, there is only one clinical trial on pegylated IFNα-2a in melanoma published yet [12].

Here we report on the results of the first prospective, open-label phase II trial combining Dacarbazine with pegylated Interferon α-2a.

Patients and Methods

Patients

Patients eligible for this clinical trial provided written informed consent and have fulfilled the following inclusion criteria:

Age ≥ 18 and ≤ 75 years, ECOG scale 0-2, confirmed metastatic melanoma (stage IV, AJCC classification) [1], at least one uni-dimensionally measurable lesion according to RECIST criteria, minimum indicator lesion size of > 10mm, wash-out period of 4 weeks for previous inter-

feron treatment. Patients with adjuvant previous interferon treatment were accepted, but not those with pegylated interferon treatment or those with tumor progression to stage IV disease during interferon therapy. Patients with mucosal, ocular or melanoma of unknown origin were excluded. Pregnant or lactating women have not been treated. Patients should not have an evidence for brain metastases in the basic examinations. Patients with a history of malignancies other than basal cell carcinoma or squamous cell carcinoma or carcinoma in situ of the cervix were excluded. Patients with a history of severe cardiac disease (NYHA, III/IV) myocardial infarction within the last 6 months or ventricular tachyarrhythmia requiring ongoing treatment or unstable angina were not included. Further exclusion criteria: medical history of severe psychiatric diseases especially depression, seizure disorders requiring anti-convulsant treatment, history of poorly-controlled thyroid dysfunctions, known infections with hepatitis B or C or HIV, patients with immune diseases except for rheumatoid arthritis, patients with abnormal baseline hematologic laboratory parameters (Hb <10g/dl, WBC < 4/nl, platelets < 100/nl, bilirubin > 1.5 ULN (upper limit of normal), ALT/AST > 2.5 ULN, ALP > 2.5 ULN or serum-creatinin > 1.5 ULN. Patients should have a life expectancy of at least three months.

Protocol design and treatment

This 3-centre, open-label phase II study of DTIC plus pegylated Interferon α-2a was approved by the ethics committee of each participating centre and their respective authorities.

Dacarbazine (DTIC) was given intravenously at a dose of 850mg/m^2 every 3 weeks for a maximum of up to 25 weeks. Pegylated interferon α-2a was given at a dose of 180µg once weekly subcutaneously for up to 25 weeks. If subjects did not present progressive disease at the end of the 25 week period, they were allowed to continue until progression in an independent Expended Assess Program (EAP) for an undefined period of time. In the absence of NCI-CTC toxicity criteria greater than grade 1, DTIC therapy was repeated every 3 weeks, for

subjects not tolerating 180µg of pegylated interferon α-2a, the dose had been reduced to 90µg and maintained at this level, if tolerated until disease progression.

Any subject who experienced grade 2 laboratory abnormalities or adverse events should maintain on the assigned dose if possible. For subjects experiencing grade 2 elevation of ALT, pegylated interferon α-2a should be temporarily stopped. Subjects experiencing grade 2 flu-like symptoms should continue pegylated interferon α-2a and DTIC treatment. Pegylated interferon α-2a and/or DTIC should be temporarily stopped and/or reduced if a subject experienced ≥ grade 3 laboratory abnormalities (except for elevated ALT), grade 4 fever, chills or other flu-like symptoms, ≥ grade 3 adverse events (except for flu-like symptoms) or grade 2 elevated ALT.

This phase II study was initiated to evaluate the tolerability, safety and efficacy of the combined treatment regimen. The primary endpoint was the evaluation of the response rate.

Response and toxicity assessment

All patients had dense follow-up evaluation during the study conduction. Tumor response was assessed using the RECIST criteria [13]. Patients with objective responses (CR and PR) were re-evaluated by an independent radiological (Prof. Dr. Delorme, Radiology Department, DKFZ Heidelberg, Germany). At initiation, in weeks 9, 17 and 25 and at the follow-up visits thereafter, the following imaging evaluations were used: brain CT or MRI, CT of the chest and abdomen, lymph-node ultrasound and bone scintigraphy. Other investigations have been used if clinically indicated. Patients received questions on their medical history and a complete body examination including vital signs and ECG (if mandatory). The performance status was assessed according to the ECOG status scale. Laboratory tests included hematology, blood chemistry, urine analyses, thyroid tests and a pregnancy test in pre- and peri-menopausal women. Blood was obtained during the weekly visits for the first 4 weeks, then every 3 weeks until the end of treatment, additionally, once in week 9 and 17. Three-monthly visits were

performed thereafter in the follow-up period. The visits in week 2 and 3 could be performed outside of the study centers, for instance by the treating general practitioner. All other clinical visits were required to be done in the respective study centre.

Statistical analyses

Due to the single-arm design of the study, a conservative approach for the primary analysis of safety and efficacy was made. The definition of the analysis population and the replacement of missing values have been considered. The selection of the sample size was based on practical considerations and not on power calculations. The study was designed to prove the feasibility of combined pegylated interferon α-2a to Dacarbazine. Instead of p-values of predefined hypothesis, 95% confidence intervals (2-sided) have been calculated for the main safety and efficacy parameters. An intention to treat tolerability, safety and efficacy assessment was defined for all subjects who received at least one dose of the combination of Dacarbazine and pegylated interferon α-2a. The per-protocol analysis included all subjects who were meeting the criteria for the ITT safety population and had no major protocol violations in a way that could influence the assessment of efficacy. Major protocol violations included inadequate information on tumor response, inadequate patient compliance defined as missing of two or more consecutive doses or missing more than 20% of the projected injections at time of withdrawal and lastly treatment duration of less than 25 weeks with the exception of progressive tumor response being the reason for withdrawal.

The survival rates including time to progression and time to death were analyzed by a Kaplan-Meier analysis in the intent-to-treat efficacy populations only. This type of analysis considers subjects lost to follow-up as censored observations. Additionally, more conservative survival rates have been calculated for the 3-, 6-, 9- and 12-months follow-up visits assuming subjects lost to follow-up as died at date of the last contact.

In the analysis of the safety data, the incidence of adverse events has been calculated at the preferred term level and the organ system level according to the classification of MeDRA. The same analysis has been done for the drug-related adverse events. Furthermore, adverse events were presented in individual subject listings, which included intensity, and relationship to the study drugs and were appropriate to the NCI-CTC grades.

All patients´ case report forms (CRFs) were monitored on-site at the participating centers by independent monitors.

RESULTS

Patients´ characteristics

Between August 2004 and September 2006 a total of 28 patients were included into this study. 20/28 patients (71.4%) were AJCC stage IV M1c, the remaining study patients were classified as M1b (28.6%). 39.3% of patients had an elevated LDH prior to treatment initiation. Of 16 males and 12 females with a median age of 56 years, 50% were interferon-naïve, which means they did not receive interferon as an adjuvant treatment for stage II/III. The clinical characteristics of the entire study population are summarized in table 1.

Treatment administration

A median of three cycles for DTIC and nine applications of subcutaneous pegylated interferon α-2a were given over nine weeks. The mean treatment duration was 103.5 days, the median was 62 days. The reasons for treatment discontinuation were progressive disease in all but one patients. Only one patient (ID-No. 03-02; table 1) had an adverse event-related discontinuation. The 43-year old female patient demonstrated a complete response of her lung metastases after 9 weeks (= 3 cycles) of treatment. Due to an unacceptable dizziness (CTC grade 2) she refused treatment continuation. However, at the end of the study observation period she was still in a complete remission without further treatment.

Response evaluation and survival

From 28 patients enrolled into this study, 25 were evaluable for efficacy parameters. Three patients were inevaluable due to withdrawal of study consent and refusal of any re-evaluations and follow-up investigations. Two patients (8.0%) demonstrated a complete response (CR), still lasting for more than 480 and 637 days, respectively. The CRs have been re-confirmed by an independent radiological review committee. Both patients did not receive adjuvant interferon treatment before they progressed to stage IV disease.

Four patients (16.0%) demonstrated partial responses lasting for up to 384 days (median: 236 days). The lung was the predominantly affected organ in these patients, but two of the four PRs were observed in the adrenal glands, peritoneum and skin, too. Two of the four patients received adjuvant interferon treatment, but only one progressed during this treatment to stage IV melanoma.

In one patient, a stabilized disease for 56 days was observed. This patient was interferon-naive prior to the study initiation. The median time to first response was 67.5 days, the duration of response 236 days. Progression-free survival was calculated as 56 days in median. The median overall survival time was 403 days. Details on the outcome parameters are shown in table 2.

Safety evaluation

All 28 patients included into the study were evaluable for safety parameters. Table 3 is summarizing all treatment-related adverse events showing the most intensive severity. There was only one grade 4 leucopenia, which spontaneously resolved after interruption of interferon treatment. All grade 3 events recovered after dose delays or treatment discontinuation due to progressive disease, too. Dose reductions of pegylated interferon α-2a were performed in 7

patients (28%), while 3 patients (12%) needed dose reductions for DTIC. Life-threatening adverse event were not observed.

DISCUSSION

Pegylation of therapeutic proteins is a well established method for delaying clearance and reducing protein immunogenicity. Pegylated proteins have been demonstrated to be safe and effective in humans [9]. Pharmacokinetic and pharmacodynamic data obtained from animals and a phase I study in healthy volunteers indicated that pegylated interferon α-2a injected once a week has potential for superior efficacy for hepatitis as compared to conventional interferon injected three times a week (Roche Pharma AG, investigator broschure). Studies with pegylated interferon α-2a in renal cell cancer (RCC) and chronic myeloid leukemia (CML) yielded an overall response rate of 13.4% and a median overall survival of 16 months for monotherapy (RCC) [14] and a major cytogenetic response in 35% for pegylated interferon α-2a compared to 18% for standard interferon treatment (CML) [15], respectively. Side effects of pegylated interferon α-2a were comparable with conventional interferon α-2a with a trend in favor for the pegylated interferon [15].

The only study in metastatic melanoma compared three different dose cohorts of pegylated interferon α-2a in 150 patients. An open-label, randomized, phase II trial evaluated the safety, tolerability and efficacy of subcutaneous PEG-IFNα-2a in patients with stage IV metastatic melanoma. PEG-IFNα-2a was administered subcutaneously at 180µg, 360µg, or 450µg for a maximum of 24 weeks. Response rates between 6 and 12% and an overall survival between 217.5 and 322 days were obtained for the three dosing groups. PEG-IFNα-2a at 180µg was tolerated by most patients, but treatment withdrawals were more pronounced in the 360 and 450µg dose groups (19% and 16%) in contrast to the 180µg PEG-IFNα-2a group (6%) [12].

Although there was a trend to a higher response rate and longer survival for the high-dose groups (360µg and 450µg pegylated interferon α-2a) compared to 180µg once weekly, it was questionable whether this was linked to the dose levels or to different patients´ characteristics in the three groups [12]. Since the dose-response relationship was unclear and serious adverse events leading to withdrawal of patients were more often seen in the higher dose level, 180µg once weekly pegylated interferon α-2a was chosen for this clinical trial combined with a chemotherapeutic agent, Dacarbazine. It was hypothesized that the improved pharmacokinetic profile of pegylated interferon α-2a in conjunction with Dacarbazine may increase the tumor response rates and possibly the survival rate without increasing toxicity.

Our study is the first trial combining pegylated Interferon α-2a with standard-dosed Dacarbazine in metastatic melanoma. The response rate of 24 % is interesting because the majority of patients (71.4%) suffered from stage M1c and furthermore, half of the patients were already pre-treated with conventional interferon α in the adjuvant setting. All responses (2 CRs and 4 PRs) have been confirmed by an independent review.

Of six patients with clinical responses and one patient with a stabilized disease as best response only two patients were not interferon-naïve and only one patient demonstrated a progression during adjuvant interferon treatment. Six of seven patients with a tumor progression during adjuvant conventional interferon treatment showed also a progressive disease during pegylated interferon α2a therapy. However, it is still speculative to argue that the probability of a clinical benefit from pegylated interferon α2a is higher in interferon-naïve patients. The interpretation of our trial results is limited due to the relatively low number of patients included into this phase II trial. Of interest, the results of our trial confirm that durable complete responses can be found in studies combining conventional chemotherapeutic agents with pegylated interferon α. A meta-analysis of more than 3000 patients from multiple randomized trials by Huncharek et al concluded that the combination of Dacarbazine with conventional

interferon α is capable of producing response rates greater than with DTIC monotherapy alone [8]. However, the impact on the overall survival time is still unclear and needs clearly to be demonstrated in a phase III trial design.

Temozolomide has also been combined with conventional interferon α. A prospective-randomized phase III trial from Germany and Switzerland compared the combination to Temozolomide alone. Kaufmann et al demonstrated 13.4% partial or complete remissions in the monotherapy arm in contrast to 24.1% for Temozolomide and conventional interferon α2b. There was only a slight trend to an improvement of overall survival which accounted for 8.4 months for single-agent treatment versus 9.7 months for the combination [16].

Since our phase II trial was not comparing different regimens, it is difficult to draw final conclusions. However, it is obvious that the safety profile of combined pegylated interferon α-2a and Dacarbazine is convenient with few grade 3 and 4 toxicities. Also, the number of discontinuations due to treatment-related adverse events was comparably low. In the single-agent pegylated IFNα2a trial of Dummer et al, dose reductions or dose delays due to adverse events or laboratory abnormalities occurred in 23% of the patients treated in the 180µg group. 6% of the patients needed a treatment withdrawal in this group [12].

In conclusion, it seems that the combination with Dacarbazine is not significantly adding to the toxicity of pegylated interferon α-2a alone and is well-tolerated in general. However, the combination of Dacarbazine with pegylated interferon α-2a enhances the single-agent activity of pegylated interferon α-2a significantly. It can not be excluded that patient selection plays a role for the promising response rate in this relatively small phase II trial performed in only three melanoma centers. However, 71.4% of our patients were belonging to stage M1c and none of the patients to M1a. Interestingly, in this clinical trial six out of seven patients with clinical responses or stabilization were either interferon-naive or failed to progress to stage IV disease during adjuvant interferon treatment. This observation indicates the need of further

investigation of predictive criteria of a treatment response to interferons. The finding of this pilot trial could eventually lead to a careful consideration of the pre-treatment modalities in forthcoming, interferon-based, first-line trials for stage IV melanoma patients.

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Conflict of interest statement:

Prof. Axel Hauschild, Prof. Reinhard Dummer and Prof. Dirk Schadendorf received consulting fees and honoraria from Roche Pharma AG (Grenzach-Wyhlen, Germany). The other authors don´t have a conflict of interest to disclose.

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TABLES

Table 1
Overview on 25 evaluable patients: characteristics and treatment outcome

Pat-ID	Age / Gender	Adj. IFN yes[*1]/no	AJCC stage IV subcategories	LDH	Metastases localizations	Best response	Response duration	Survival time [days]
01-01	48 / M	no	M1c	Normal	Head and Neck, Liver, Lung, Lymph Node	PD		64
01-02	63 / F	no	M1c	Normal	Liver, Lung, Spleen	PD		224
01-03	47 / F	no	M1b	Normal	Lung	PD		716
01-05	60 / M	no	M1c	Elevated	Bone, Liver, Lung	PD		144
01-06	67 / M	yes[*1]	M1b	Normal	Lung	PD		403
01-07	68 / M	no	M1b	Normal	Lung	PD		288
01-08	67 / M	yes[*1]	M1b	Normal	Lung	PD		408
01-09	68 / M		M1c	Elevated	Liver, Lung, Lymph Node	PD		Lost to follow up after 138 d
01-10	57 / F	yes[*1]	M1c	Normal	Lung, Lymph Node	PD		629+ (alive)
01-11	56 / M	yes[*1]	M1c	Elevated	Liver, Lymph Node	PD		166
02-01	49 / F	yes[*1]	M1b	Normal	Lung	PR	3	472
02-02	69 / M	yes	M1c	Elevated	Adrenals, Lung, Lymph Node, Retroperitoneal mass, Skin	PR	88	366
02-03	47 / M	no	M1c	Normal	Adrenals, Lung, Lymph Node, Peritoneum, Skin	PR	384	560
02-04	48 / M	yes[*1]	M1c	Normal	Liver, Lung, Lymph Node, Skin	PD		725
02-05	47 / F	no	M1c	Elevated	Bone, Breast, Lung, Retrop-eritoneal mass, Skin	PD		222
02-06	42 / M	yes	M1c	Normal	Lung, Lymph Node	PD		408
02-07	43 / F	yes	M1c	Normal	Ascites, Lung, Lymph Node	SD	56	608+ (alive)
03-01	43 / F	no	M1b	Normal	Lung	CR	637 + (ongoing)	746+ (alive)
03-02	49 / F	yes	M1c	Elevated	Bone, Lung, Lymph Node, Muscles	PD		273
03-03	58 / M	yes	M1c	Elevated	Colon, Lymph Node, Mus-	PD		567+ (alive)

					cles, Skin			
03-04	60 / M	no	M1b	Normal	Lung	PD		322
03-05	43 / F	no	M1c	Elevated	Bone, Liver, Lymph Node	PD		86
03-06	47 / F	yes[*1]	M1c	Elevated	Bone, Breast, Colon, Lung, Muscles	PD		145
03-07	68 / M	no	M1b	Normal	Lung, Muscles	PR	73	384
03-08	58 / M	no	M1c	Elevated	Lung	CR	480 + (ongoing)	588+ (alive)

[*1]Patients with progressive disease leading to stage IV during adjuvant interferon treatment

Table 2

Efficacy evaluation (25 patients)

Best response	n	%
CR	2	8.0
PR	4	16.0
SD	1	4.0
PD	18	72.0
Total	25	100.0

Outcome	n	Median (days)	Range (days)
Time to first response (CR + PR)	6	67.5	57-113
Duration of response (CR + PR)	6	236	3-637
Time to progressive disease	23	57	52-449
Progression free survival (PFS)	25	56	55-71 (95% CI)
Overall survival	25	403	237-560 (95% CI)

Table 3
Treatment-related AE's (NCI-CTC criteria), most intensive severity per AE and patient (n=28)

Adverse events	Total	Mild/ grade 1	Moderate/ grade 2	Severe/ grade 3	Life-threatening/ grade 4
	n	n	n	n	n
Leucopenia/Neutropenia	10	.	8	1	1
Nausea	9	4	5	.	.
Headache	5	.	3	2	.
Diarrhea	4	4	.	.	.
Dizziness	4	2	1	1	.
Fatigue	4	1	2	1	.
Back pain	3	2	1	.	.
Depression	3	2	1	.	.
Hyperhidrosis	3	1	2	.	.
Myalgia	3	1	1	1	.
Parosmia	3	2	1	.	.
Thrombocytopenia	3	2	.	1	.
Vomiting	3	.	3	.	.
Alopecia	2	1	1	.	.
Anorexia	2	1	1	.	.
Influenza	2	2	.	.	.
Pyrexia	2	2	.	.	.
Rigors	2	1	1	.	.
Abdominal pain	1	.	1	.	.
Increased liver enzymes	1	.	.	1	.
Anemia	1	.	1	.	.
Constipation	1	.	1	.	.
Dysgeusia	1	1	.	.	.
Gamma-GT increase	1	.	.	.	.
Hiccups	1	.	.	.	.
Infusion site swelling	1	1	.	.	.
Keratoconjunctivitis sicca	1	1	.	.	.
Nasopharyngitis	1	1	.	.	.
Pain in extremity	1	.	.	.	.
Palpitations	1	.	.	.	.
Photosensitivity reaction	1	1	.	.	.
Rash	1	1	.	.	.
Sneezing	1	1	.	.	.
Purulent sputum	1	.	.	.	.
Vertigo	1	.	.	.	.
Blurred vision	1	.	.	.	.
Decreased weight	1	.	.	.	.